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EFFECT OF ISCHEMIA ON SEROTONIN METABOLISM IN CEREBRAL CORTEX

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Adult, male Sprague-Dawley rats subjected to 15 minutes of temporal unilateral common carotid artery occlusion and up to 6 hours of re-circulation was employeed. The cortical concentration of serotonin (5-HT) and its metabolite were determined by High Performance Liquid Chromatography with electrochemical detection. After 6 hours of recirculation, diminution of serotonin (5-HT) and accumulation of 5-hydroxyindoxleacetic acid (5-HIAA) in ischemic cortex were detected. This finding strongly suggests that a postischemia increase release and turnover of serotonin, which may explain postischemic vasoconstriction.

Key words : Delayed postischemic hypoperfusion,serotonin, 5-hydroxyindoleacetic acid.

INTRODUCTION

Patients with ischemic stroke often deteriorate while being observed hours or even days after the initial ictus. Delayed deterioration could be prevented if the responsible pathologic processes were understood.Release of vasoactive amines, formation of vasoactive products of arachidonic acid metabolism, and disturbance of calcium ion homeostasis in cerebrovascular smooth muscle may attribute to postischemic vasoconstriction[1]. During the past decade, there has been a surge of interest in the possibile relationship between brain monoamines and ischemic brain insults. Monoamine transmitters may play an important role in postischemic cerebral dysfunction. Monoamine may regulate cerebral reperfusion after ischemic insult and influence the recovery of brain ischemia.

The purpose of this investigation was to examine the change of serotonin (5－HT) and 5－hydroxyindoleacetic acid (5－HIAA) in cerebral ischemia, we have measured tissue level of 5－HT and 5－HIAA in cerebral cortex of rat after transient ischemia. If 5－HT do attribute to the morbidity of postischemic cerebral dysfunction, such change should be evidence at this time.

MATERIALS AND METHODS

Adult, male Sprague－Dawley rats weighting 250－300 gm were used. Animals were caged (three per cage) at constant temperature (about 27℃) in simulated day and night condition for 3 weeks prior to study and allowed free access to drinking water and chow.

The rats were anesthesized with ketamine hydrochloride (ketalar, 100 ㎎ / ㎏ intraperitoneally). Left common carotid artery were exposed through ventral midline incision and artery, isolated from adjacent nerves and vessels and clipped with Sugita aneurysm clip for 15 minutes, then was release. The animals were killed by dacapitation 6hrs after transient ischemia. The heads were severed, cooled in an ice bath, and the brains were removed (Lt: ischemia). Another group of rats subjected to sham operation without clipping the left common carotid artery. The concentration of serotonin (5－HT) and 5－hydroxyindoleacetic acid (5－HIAA) were analyzed by High Performance Liquid Chromatography with electrochemical detection (HPLC, Waters)[2].

All values obtained from this experiment are expressed as mean±SEM. The significance between control and experimental data was determined by Student's t test.

RESULTS

The concentrations (mean±SEM) of 5-HT in control and ischemic cortex were 268±20 and 108±18 ng per gram, (n=8) respectively, the difference is statistically significant ($P<0.005$) .The concentrations (mean±SEM) of 5-HIAA in control and ischemic cortex were 574±26 and 964±16 ng per gram, ($P<0.005$). Sham operation did not alter the levels of 5-HT and 5-HIAA: the concentration of 5-HT and 5-HIAA in these rats were 254±26 and 582±36 ng per gram, (n=5) respectively.

DISCUSSION

In the recirculation period following cerebral ischemia, an initial "reactive" hyperemia is succeeded by a secondary decrease in cerebral blood flow (CBF), called delayed postischemic hypoperfusion[3~9]. Cerebral recovery may be hindered by poor perfusion rather than by immediate death of hypoxic nerve cells. The hyperemia may be explained by vasodilation due to tissue acidosis from lactic acid and carbon dioxide, or by a slight increase in extracellular potassium[11~13]. Fluorescent histochemical technique have demonstrated 5-HT in axon terminals of the cerebral cortex, to which they project from brainstem neurons. Some investigators have assigned a regulatory role in cerebral blood flow (CBF) to 5-HT, and this concept has been supported by observed effects of 5-HT on pial vessel diameter[14]. On the basis of the vasoactive properties of 5-HT, it has been speculated that the increased turnover of this amine could lead to a deleterious vasconstriction, which might cause additional cellular damage[15].

This study showed that deprivation of blood supply to the brain led to reduction of 5-HT concentration in the cerebral cortex. This reduction is due to the increased release of this monamine, since the rates of its synthesis and degradation are depressed after vascular occlusion. 5-HIAA concentration is increased in the brain following vascular occlusion, it is possibile that 5-HIAA increased as the result of

increased metabolism of 5－HT release from its stores. Wurtman and Zervas[16] have postulated that an inappropriate loss of monamine neurotransmitters may exacerate the pathophysiologic changes caused by initial ischemia. Reduction of 5－HT concentration in cerebral cortex appeared at the time when adenosine triphosphate levels already were reduced for a long period. Unlike many other cell types, neuron in vivo appear incapable of using any other substance than glucose as their main energy source. Under normal circumstances, adenosine triphosphate, the energy source for the maintance of the electrochemical gradients, is efficiently produced through aerobic glycolysis and oxidative phosphorylation. Cerebral ischemia which is characterized by deprivation of glucose and oxygen supply to the brain, inevitable led to ATP depletion.Therefore, it appears that release of 5－HT in the brain is most probably related to a failure of the neuronal energy stores and the membrane transport following vascular occlusion[17]. Welch, Hashi and Meyer[18] have suggested that a fall in 5－HT reflects release of transmitter 5－HT into the extracellular fluid where it may have the effect of limiting capillary perfusion by vasoconstricting small vessels. The post－ischemic disruption of flow and metabolism, therefore, creates a potential for further brain damage. This secondary change might be prevented by appropriate therapeutic intervention because it occurs at time when patient are often under medical supervision.

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腦缺血對大腦皮質 Serotonin 代謝的影響

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摘　要

雄性大白鼠左側頸總動脈以血管夾夾住十五分鐘後釋放，於再循環六小時後斷頭取出其大腦，以High Performance Liquid Chromatography with electrochemical detection 測量左、右大腦皮質 Serotonin （5－HT）及其代謝物 5－hydroxyindoleacetic acid（5－HIAA）的濃度。結果左側缺血大腦皮質5－HT含量減低而其代謝物5－HIAA含量增加，對照組大腦皮質並無明顯變化。由此實驗結果，可認爲腦缺氧後Serotonin的釋放及轉變的增加是造成腦缺血後血管收縮的原因。